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(54) Title: SYNTHESIS OF [R-(R*,R*)]-2-(4-FLUOROPHENYL)-BETA.DELTA-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID HEMI CALCIUM SALT (ATORVAS-TATIN)

(57) Abstract: The present invention discusses a novel process for the synthesis of [R-(R*,R*)]-2-(4-fluorophenyl)-B.D-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt by using 4-fluoro- α -[2-methyl-1-oxopropyl]- γ -oxo-N- β -diphenylbenzene butanamide with (4R)-methyl 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-3-acetate. The compound so prepared is useful as inhibitors of the enzyme HMG-CoA reductase and are thus used as hypolipidemic and hypocholesterolemic agents.

TITLE OF THE INVENTION:

SYNTHESIS OF [R-(R*,R*)]-2-(4-FLUOROPHENYL)-BETA, DELTA-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID HEMI CALCIUM SALT (ATORVASTATIN)

5

FILED OF THE INVENTION:

This invention relates to a process for manufacturing R-(R*,R*)]-2-(4-fluorophenyl)-B,D-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid
10 hemi calcium salt, atorvastatin and the novel intermediates produced during the course of manufacture. The said compound is useful as inhibitors of the enzyme HMG-CoA reductase and are thus useful as hypolipidemic and hypocholesterolemic agents.

BACKGROUND OF THE INVENTION

15 US Patent. No. 4,681,893, discloses a route using resolution of the racemic product using R (+) α -methyl benzyl amine. US patent No. 5,003,080 discloses a synthetic route for the preparation of the chiral form of atorvastatin. The patent discloses a process for the preparation of the lactone or its salts by coupling an ester of (4R)-6-
20 (2-aminoethyl)-2,2-dialkyl-1,3-dioxane-3-acetate with 4-fluoro- α -[2-methyl-1-oxopropyl] γ -oxo-N- β -diphenylbenzenebutaneamide followed by deprotection and hydrolysis to give the product. The product suffers from the fact ozonolysis is required as one of the steps for the synthesis of the amino ketal intermediate, which is hazardous
25 for large scale preparation. The patent describes an alternate procedure wherein 4-fluoro- α -[2-methyl-1-oxopropyl] γ -oxo-N- β -diphenylbenzenebutaneamide is reacted with 3-amino propinaldehyde acetal followed by conventional procedures to give atorvastatin.

US patent No. 5,216,174, No. 5,097,045, No. 5,103,024, No. 5,124,482, No. 5,149,837, No. 5,155,251, No. 5,216,174, No. 5,245,047, No. 5,273,995, No. 5,248,793, and No. 5,397,792 describes various minor modifications in the procedure for the preparation of
5 atorvastatin calcium salt.

Synthesis of esters of (4R)-6-(2-aminoethyl)-2,2-dialkyl-1,3-dioxane-3-acetate is an important part of the preparation of atorvastatin calcium. US patent 5,155,251 also discloses a synthetic route for the synthesis of (3R)-4-cyano-3-hydroxy butyric acid esters
10 from (S)-3-hydroxy butyrolactone, which in turn is synthesized from a suitable carbohydrate substrate.

Other patents like 5,292,939, 5,319,110 and 5,374,773 discloses the preparation of 3,4-dihydroxybutyric acid. However, isolation of this highly water soluble compound or its lactone is not
15 attempted.

Another multi step procedure starting from (S)-malic acid (J. org. Chem., 1981, 46, 4319) is reported. Esters of (S)-malic acid have also been used (Chem. Lett., 1984, 1389) for the synthesis of the hydroxy lactone involving BMS-NaBH_4 reduction, followed by
20 lactonization. While a six step procedure from D-isoascorbic acid is also reported (Syn., 1987, 570) but this process requires a silica gel chromatographic separation of the diastereomeric mixtures.

Optical resolution of the racemic hydroxylactones using lipase is disclosed in US patent 5,084,392 but this method suffers from poor
25 enantiomeric excess and loss of the other active isomer.

Thus, these prior art procedures involves cumbersome reaction conditions or expensive starting materials, reagents which are difficult to handle or hazardous for scale up, coupled with a multi step procedure which results in poor overall yield.

The object of the present invention is to disclose an inexpensive, simple and scalable route for the synthesis of atorvastatin.

To achieve the said objective, this invention provides a process
5 involves the synthesis of compound R-(R*,R*)]-2-(4-fluorophenyl)-
B,D-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)
carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (formula
XXII) comprising:

- 10 a) reacting of compound of formula XVII with a compound
of structure XIV in a non-polar solvent, to give an
intermediate of structure XXI,
- b) deprotection, followed by hydrolysis of the compound of
structure XXI followed by cyclization in ethyl acetate to
give the lactone,
- 15 c) treating the lactone with NH₃ to give the ammonium salt,
and
- d) reacting the ammonium salt with CaCl₂ gives the
corresponding calcium salt of formula XXII.

20 The non-polar solvent in step (a) is selected from xylene or
acetonitrile.

The de-protecting agent in step (b) is selected from moist silica
or PTSA.

The ammonium salt in step (c) is prepared by treating with
aqueous NH₃ or methanolic NH₃ or by passing NH₃ gas to the
25 compound taken in EtOAc, MeOH, isopropyl alcohol, diisopropyl
ether or cyclohexane.

The compound of formula XVII is prepared by:

- a) reacting meldrum acid with isobutyryl chloride in the presence of base in CH_2Cl_2 to give an intermediate of formula XVIII,
- b) reacting the intermediate of formula XVIII with base in CH_2Cl_2 to give an intermediate of formula XIX,
- c) reacting the intermediate of formula XIX with benzaldehyde in the presence of base and toluene to give a compound of formula XX, and
- d) reacting of compound of formula XX with 4-fluorobenzaldehyde with a metal cyanide and polar solvent in the presence of a base to give the compound of formula XVII.

In step (b) the base is selected from aniline, pyridine, triethylamine, dimethylaniline, diethylisopropylamine.

- 15 In step (c) the base is selected from piperidine, pyrrolidine or diisopropylethylamine.

In the metal cyanide in step (d) is selected from NaCN, CuCN, KCN, AgCN or tetraalkyl ammonium cyanide.

- 20 The polar solvent in step (d) is selected from DMSO, DMF, CH_3CN .

The base in step (d) is selected from diisopropylethyl amine, 1-methylimidazole, pyridine.

The compound of (4R)-methyl 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-3-acetate (Formula XIV) used in step (a) is prepared by:

- 25 a) reacting a compound of formula II with meldrum's acid followed by hydrolysis to give a compound of formula III,
- b) reacting a compound of formula III with thionyl chloride to give an acid chloride which is then reacted with a meldrum's acid followed by alcoholysis to give a compound of formula IV.

c) reducing a compound of formula IV to give a compound of formula V,

d) reducing a compound of formula V to give a dihydroxy ester of formula VI,

5 e) converting a compound of formula VI to give a compound of formula VII,

f) ammonolysis of a compound of formula VII to give a compound of formula VIII,

10 g) alternatively reacting the compound of formula VII with phthalimide salt to give a compound of formula XVI,

h) reacting a compound of formula XVI with hydrazine hydrate to give the compound of formula VIII, and

i) where R_5 = *tert*-butyl in formula VIII, formula XIV is obtained

15 R_4 in step (a) is chosen from. OMs, OTs, Br, Cl or I.

The alcohol in step (b) is chosen from methanol, ethanol, isopropanol, benzyl alcohol.

The reducing agent in step (c) is baker's yeast or a reagent of formula R^*_2BCl where R^*_2 is chosen from (-) α pinene or (+) α -pinene.

20 The reducing agent in step (d) is chosen from dimethoxyethylboron or triethoxyboron and sodium borohydride.

The protecting group for conversion in step (e) is chosen from acetone, benzophenone, acetophenone or benzaldehyde.

The reagent for ammonolysis in step (f) is chosen from aqueous
25 NH_3 , methanolic NH_3 or gaseous NH_3 in a solvent chosen from EtOAc, cyclohexane, methanol, isopropanol or diisopropyl ether.

The phthalimide salt in step (g) is chosen from potassium, sodium or lithium.

The compound of (4R)-methyl 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-3-acetate (Formula XIV) used in step (a) is prepared by:

- a) reacting a compound of formula II with meldrum's acid followed by hydrolysis to give a compound of formula IX,
- 5 b) reacting a compound of formula IX with tert-butyl acetate with a base at -30 to -80°C to give a compound of formula X,
- c) reducing a compound of formula X to give a compound of formula XI,
- d) reducing a compound of formula XI to give a dihydroxy
10 ester of formula XII,
- e) Converting a compound of formula XII to give a compound of formula XIII,
- f) ammonolysis of a compound of formula XIII to give a compound of formula XIV,
- 15 g) alternatively reacting the compound of formula XIII with phthalimide salt to give a compound of formula XV and
- h) reacting a compound of formula XV with hydrazine hydrate to give the compound of formula VIII

20 R_4 in step (a) is chosen from, OMs, OTs, Br, Cl or I.

The reducing agent in step (c) is baker's yeast or a reagent of formula R^*_2BCl where R^*_2 is chosen from (-) α pinene or (+) $-\alpha$ -pinene.

25 The reducing agent in step (d) is chosen from dimethoxyethylboron or triethoxyboron and sodium borohydride.

The protecting group for conversion in step (e) is chosen from acetone, benzophenone, acetophenone or benzaldehyde.

The reagent for ammonolysis in step (f) is chosen from aqueous NH_3 , methanolic NH_3 or gaseous NH_3 in a solvent chosen from EtOAc, cyclohexane, methanol, isopropanol or diisopropyl ether.

The phthalimide salt in step (g) is chosen from potassium,
5 sodium or lithium.

The intermediate compounds of formula XVIII, XIV, XV, VII & IX whenever prepared by the above process.

The intermediate of formula VII, wherein R_5 is chosen from C_1 - C_5 alkyl, benzyl, isopropyl, cyclohexyl or tert-butyl.

10 The intermediate of formula IX, wherein R_4 is chosen from CH_2Br , CH_2Cl , CH_2I , CH_2OMs or CH_2Ots .

DETAILED DESCRIPTION OF THE INVENTION

The process of the present invention in its first aspect is a new, improved, economical, and commercially feasible method for
15 preparing HMG CoA reductase inhibitors of Formula XXII which are useful as inhibitors of the enzyme HMG CoA reductase and are thus useful as hypolipidemic or hypocholesterolemic agents is outlined in Scheme 5.

Structure XXII

20 The synthetic scheme for the synthesis of the amino ester of formula VIII is outlined in scheme I

Scheme - 1

Thus, a halo acetic acid of formula I, where $\text{X} = \text{Cl}$, Br or I is treated with sodium or potassium salt of trifluoromethane sulfonic
25 acid or p-toluenesulfonic acid in the presence of base chosen from Et_3N , pyridine, N,N-dimethylaniline, N,N-diisopropylethyl amine, etc., in a solvent like, CH_2Cl_2 , CH_3CN , DMF etc., to give an intermediate which is then converted to an acid chloride by choosing a reagent from thionyl chloride, oxalyl chloride, PCl_5 etc in the

presence of a base chosen from Et_3N , pyridine, N,N-dimethylaniline, N,N-diisopropylethyl amine, etc., in a solvent like, CH_2Cl_2 , CH_3CN , DMF etc., to give a compound of formula II, which is subsequently treated with meldrum's acid in presence of pyridine and CH_2Cl_2 to give an acyl meldrum acid which is hydrolyzed to give a compound of formula III.

A β -keto acid of formula III is then converted to its acid chloride by reacting with a reagent chosen from PCl_5 , oxalyl chloride, thionyl chloride etc., in the presence of a base chosen from pyridine, Et_3N , diisopropylethyl amine, N,N-dimethylaniline etc., in a solvent chosen from CH_2Cl_2 , CH_3CN , DMF etc. to give an acid chloride which is then reacted with meldrum acid as described earlier to give an acyl meldrum acid which on subsequent reaction with an alcohol R_5OH

Where $\text{R}_5 = \text{C}_1\text{-C}_6$ alkyl, C_3 to C_6 -cycloalkyl, benzyl etc., to give an intermediate of formula IV.

The diketo ester compound of formula IV is then reduced either with baker's yeast or with a reagent of formula R^*_2BCl

Where R^*_2 is chosen from (-)- α -pinene, (+)- α -pinene, etc., to give a hydroxy keto ester of formula V. A hydroxy ketone ester of Formula V is treated with a borane reagent of formula $\text{R}_2^{10}\text{BOCH}_3$ wherein R^{10} is a alkyl group of C1 to 3, for example, methoxydiethylborane in the absence of air and subsequent treatment with a metal hydride, such as, for example, sodium borohydride in a solvent, such as, for example, methanol, tetrahydrofuran, mixtures thereof, and the like at about 0°C . to about -110°C . for about 5 hours followed by subsequent treatment with an acid, such as, for example, glacial acetic acid, and the like to afford a compound of Formula VI.

Preferably, the reaction is carried out with methoxydiethylborane under a nitrogen atmosphere and subsequent treatment with sodium borohydride in a mixture of methanol and tetrahydrofuran at about -20°C . to about -78°C . for about 5 hours followed by the addition of
5 glacial acetic acid.

A 3,5-dihydroxy ester of Formula VI is treated with a ketal-forming reagent of



wherein R^1 or R^2 is independently from C_1 to C_3 alkyl, phenyl,
10 benzyl, substituted phenyl etc., for example, a ketal-forming reagent selected from acetone, 2,2-dimethoxypropane, 2-methoxypropene, cyclopentanone, cyclohexanone, 1,1-dimethoxycyclopentane, 1,1-dimethoxycyclohexane, and the like or optionally an acetal forming reagent, for example, benzaldehyde, and the like in the presence of an
15 acid, such as, for example, methanesulfonic acid, camphorsulfonic acid, paratoluenesulfonic acid, and the like, in the presence of excess reagent or in an inert solvent, such as, for example, dichloromethane, and the like at about 0°C . to about the reflux temperature of the reagent or solvent to afford a compound of Formula VI wherein R^1
20 and R^2 are as defined above. Preferably, the reaction is carried out with a ketone forming reagent of Formula VII, for example, 2,2-dimethoxypropane and acetone in the presence of methanesulfonic acid at room temperature.

A compound of formula VII, which is then taken up in a
25 solvent like, methanol, EtOAc, hexane or a mixture of these solvents and is converted to a compound of formula VIII by treating with gaseous NH_3 or by treating with aqueous NH_4OH solution or methanolic ammonia to give a compound of formula VIII

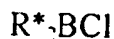
Optionally a compound of formula XIV can be prepared as described in scheme 2

Scheme - 2

5 Thus a compound of formula II where, $R = CH_2Br, CH_2Cl, CH_2I, CH_2OMs, CH_2OTs$, etc., with meldrum acid in the presence of a base chosen from pyridine, Et_3N , N,N -dimethylaniline, N,N -diisopropylethylamine etc in CH_2Cl_2 to give an acyl meldrum acid of formula IX.

10 The acyl meldrum acid is taken in a solvent selected from hexane, THF, ether, or a mixture of hexane, THF or ether and was cooled to -30 to $-80^\circ C$. A solution of tertiary butyl acetate and a base chosen from $n-BuLi$, LDA, Lithium pyrrolidide, etc., is added at a temperature between -30 to $-80^\circ C$ to afford the diketo ester compound of formula X.

The diketo ester compound of formula X is then reduced either with baker's yeast or with a reagent of formula



Where R^*_2 is chosen from $(-)\alpha$ -pinene, $(+)\alpha$ -pinene, etc., to give a hydroxy keto ester of formula XI. A hydroxy ketone ester of Formula XI is treated with a borane reagent of formula $R_2^{10}BOCH_3$ wherein R^{10} is a alkyl group of C1 to 3, for example, methoxydiethylborane in the absence of air and subsequent treatment with a metal hydride, such as, for example, sodium borohydride in a solvent, such as, for example, methanol, tetrahydrofuran, mixtures thereof, and the like at about $0^\circ C$, to about $-110^\circ C$, for about 5 hours followed by subsequent treatment with an acid, like glacial acetic acid, and the like to afford a compound of Formula XII. Preferably, the reaction is carried out with methoxydiethylborane under a

nitrogen atmosphere and subsequent treatment with sodium borohydride in a mixture of methanol and tetrahydrofuran at about 20°C. to about -78°C. for about 5 hours followed by the addition of glacial acetic acid.

5 A 3,5-dihydroxy ester of Formula XII is treated with a ketal-forming reagent of



wherein R^1 or R^2 is independently from C_1 to C_3 alkyl, phenyl, benzyl, substituted phenyl etc., for example, a ketal-forming reagent
10 selected from the group consisting of acetone, 2,2-dimethoxypropane, 2-methoxypropene, cyclopentanone, cyclohexanone, 1,1-dimethoxycyclopentane, 1,1-dimethoxycyclohexane, and the like or optionally an acetal forming reagent, for example, benzaldehyde, and the like in the presence of an acid, such as methanesulfonic acid,
15 camphorsulfonic acid, paratoluenesulfonic acid, and the like, in the presence of excess reagent or in an inert solvent, such as, for example, dichloromethane, and the like at about 0°C. to about the reflux temperature of the reagent or solvent to afford a compound of Formula XIII wherein R^1 and R^2 are as defined above. Preferably, the
20 reaction is carried out with a ketone forming reagent, for example, 2,2-dimethoxypropane and acetone in the presence of methanesulfonic acid at about room temperature.

A compound of formula XIII, which is then taken up in a solvent like, methanol, EtOAc, hexane or a mixture of these solvents
25 and is converted to a compound of formula XIV by treating with gaseous NH_3 , or by treating with aqueous NH_4OH solution or methanolic ammonia.

Alternatively, the intermediate of formula VII or XIII can be converted to VIII and XIV respectively as shown in scheme 3

Scheme - 3

where R_6 is chosen from Li, K, Na, quaternary ammonium etc., to give the substituted phthalimide of formula XV or XVI which on treatment with hydrazine hydrate gives the desired amino compound.

- 5 A amino ester of Formula VIII or XIV is reacted with a diketone of Formula XVII wherein the process for the preparation of the compound of formula XVII is described in scheme 4

Scheme - 4

- 10 A compound of formula XVII is prepared as described in scheme 6, which comprises of reacting isobutyryl chloride and meldrum's acid in the presence of a base chosen from pyridine, triethylamine, diisopropylethyl amine, dimethylaniline etc in CH_2Cl_2 at 0-5°C for about 18h to give an intermediate of formula XVIII.
- 15 Preferably the reaction is done in pyridine and CH_2Cl_2 at 0°C. The acyl meldrum acid so obtained is then reacted with aniline in a solvent chosen from CH_2Cl_2 , acetonitrile, toluene etc., at the reflux temperature of the solvent for about 12h to afford the amide of formula XIX. Preferably the reaction is carried out in CH_2Cl_2 by stirring at room temperature.
- 20

- The keto amide is then reacted with benzaldehyde in the presence of a base chosen from aqueous NaOH in acetic acid, sodium acetate and acetic acid, pyrrolidine and acetic acid, piperidine and toluene, pyrrolidine and toluene etc., at the reflux temperature and by
- 25 removal of water for about 26h to give the methylenepheryl intermediate of formula XX.

The compound of formula XX is treated with 4-fluorobenzaldehyde in the presence of a catalyst chosen from metallic cyanide where the metal is Ag, K, Na, Cu, tetraalkylammonium etc..

or trimethylsilyl cyanide in a polar solvent chosen from DMSO, DMF, acetonitrile etc., at the reflux temperature of the solvent to give a compound of formula XVII. Preferably the reaction is carried out by reacting 4-fluorobenzaldehyde and sodium cyanide in DMSO at
5 reflux temperature.

The diketone of formula XVII is reacted with the amino ester of formula VIII or XIV as described in Scheme 5 in the presence of a catalyst of Formula $R_{12}CO_2H$ wherein R_{12} is chosen from trifluoromethane sulfonic acid, methane
10 sulfonic acid, p-toluene sulfonic acid and a solvent or mixtures thereof such as, for example, acetonitrile, xylene, diisopropyl ether and the like for about 24 to about 48 hours from 5 to 10°C to about the reflux temperature of the solvent with the removal of water to afford a compound of Formula VII. Preferably, the reaction is carried out in
15 the presence of methanesulfonic acid and a mixture of xylene-hexane at reflux for about 48 hours with the removal of water.

Scheme – 5

The compound of formula XXI is converted to atorvastatin
20 calcium as shown in scheme 6

Scheme – 6

Which involves the deprotection of the ketal followed by hydrolysis of the ester to give the free acid which is converted to its
25 ammonium salt by reacting with either NH_4OH , methanolic NH_3 or by bubbling gaseous NH_3 to the solution of carboxylic acid in a solvent chosen from a mixture of EtOAc, hexane, diisopropyl ether, isopropanol, cyclohexane and methanol. Preferably the intermediate of formula XXI is de-protected using moist silica in CH_2Cl_2 at room

temperature over a period of 24h and is then hydrolyzed using methanolic sodium hydroxide and acidified using dil HCl to give the free acid which is converted to its ammonium salt by passing gaseous NH_3 in EtOAc. The ammonium salt is then treated with calcium acetate to give atorvastatin calcium.

The invention will now be described with reference to the following example.

Example 1

1.1 Preparation of 4-methyl-3-oxo-N-phenylpetanamide (Formula XIX).

To a suspension of malonic acid (104g) in acetic anhydride (120mL) at room temperature, Conc. H_2SO_4 (3mL) was added. The mixture was cooled to 20°C followed by the addition of acetone (80mL) drop wise. The contents were stirred at room temperature (15min) and kept at $0-5^\circ\text{C}$ overnight and filtered. The solid was washed with cold water and cold acetone and dried. The crude material was recrystallized from acetone-hexane mixture.

Meldrum's acid (59g) was dissolved in CH_2Cl_2 (200 mL) and cooled to 0°C . Pyridine (73mL) was added drop wise over a period of 30 min and the mixture was stirred for an additional 10 min. Isobutyryl chloride (44g) was added drop wise over a period of 30 min. and the mixture was stirred at 0°C for 1h followed by stirring at room temperature over night. The mixture was poured into 1.5N HCl containing crushed ice. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x100mL). The combined extracts were washed with 1.5N HCl (2x100mL) followed by saturated NH_4Cl solution (2x100mL) and dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude acyl meldrum's acid which was used for the next step.

The crude acyl meldrum's acid (84g) was taken in benzene (300mL) and aniline (111mL) was added. The mixture was refluxed for 4h. Cool the reaction mixture to room temperature and wash with 2N HCl (5x100mL) and benzene was removed under reduced pressure to get formula XIX.

1.2 Preparation of 4-methyl-3-oxo-N-phenyl-2-(phenylmethylene) pentanamide (Formula XX).

The crude amide was taken in acetic acid and piperidine. To this mixture at room temperature benzaldehyde was added. The contents were allowed to stir under reflux for 2h. Pour the contents into water and extract with CH_2Cl_2 . The organic extracts were washed with bicarbonate, bisulfite solution, dried and concentrated under reduced pressure to afford the crude compound of formula XX.

1.3 Preparation of 4-fluoro- α -[2-methyl-1-oxopropyl] γ -oxo-N- β -diphenylbenzenebutaneamide (Formula XVII).

To 4-fluorobenzaldehyde in anhydrous DMF, sodium cyanide was added and the contents were refluxed for 4h. To this the intermediate from example 3 was added and the contents were stirred for an additional 18h. Usual work up affords the crude diketone compound of formula XVII.

1.4 Preparation of 4-trifluoromethanesulfonyl-3-oxo-butyric acid (Formula III).

To a solution of chloroacetic acid in pyridine at 0°C and CH_2Cl_2 , trifluoromethane sulfonyl chloride was added slowly. After the reaction was complete, oxalyl chloride was added and the contents

were refluxed for 3h and the solvent was removed under reduced pressure to give the crude acid chloride.

Meldrum's acid (59g) was dissolved in CH_2Cl_2 (200 mL) and cooled to 0°C . Pyridine (73mL) was added drop wise over a period of 30 min and the mixture was stirred for an additional 10 min. Trifluoromethanesulfonyl acetylchloride (44g) was added drop wise over a period of 30 min. and the mixture was stirred at 0°C for 1h followed by stirring at room temperature over night. The mixture was poured into 1.5N HCl containing crushed ice. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x100mL). The combined extracts were washed with 1.5N HCl (2x100mL) followed by saturated NH_4Cl solution (2x100mL) and dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude acyl meldrum's acid was hydrolyzed to give the title compound of formula III.

1.5 Preparation of methyl 6-trifluoromethane sulfonyl-5,3-dioxo-butryate (Formula IV).

The crude compound from example 5 was taken in CH_2Cl_2 and pyridine and was cooled to $0-5^\circ\text{C}$. Oxalyl chloride was slowly introduced and the contents were refluxed for 6h. The solvent was removed under reduced pressure to afford the crude acid chloride.

Meldrum's acid (59g) was dissolved in CH_2Cl_2 (200 mL) and cooled to 0°C . Pyridine (73mL) was added drop wise over a period of 30 min and the mixture was stirred for an additional 10 min. The acid chloride (44g) was added drop wise over a period of 30 min. and the mixture was stirred at 0°C for 1h followed by stirring at room temperature over night. The mixture was poured into 1.5N HCl containing crushed ice. The layers were separated and the aqueous

layer was extracted with CH_2Cl_2 (2x100mL). The combined extracts were washed with 1.5N HCl (2x100mL) followed by saturated NH_4Cl solution (2x100mL) and dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude acyl meldrum's acid was
5 refluxed in methanol to give the title compound of formula IV

1.6 reparation of methyl 6-trifluoromethane sulfonyl-5-oxo-3-hydroxybutyrate (Formula V).

To a mixture of dry bakers' yeast and glucose in boiled water
10 was stirred at ambient temperature. The crude diketo ester from example 5 was then added and the reaction mixture was stirred for an additional period 8-13h at ambient temperature. Celite was added to the reaction mixture and filtered. The celite bed was washed thoroughly with ethyl acetate and the combined ethyl acetate extracts
15 was dried and concentrated under reduced pressure to afford the title product which was used for the next step without further purification.

1.7 Preparation of (4R)-methyl 6-trifluoromethyl sulfonyl methyl-2,2-dimethyl-1,3-dioxane-4-acetate (Formula VII).

20 The crude product from example 6 was taken up in dry THF and isopropanol under nitrogen atmosphere. The solution was cooled to -78°C and a solution of diethylmethoxyborane was added. The reaction mixture was cooled to -80°C and sodium borohydride was added in portion over a period of 4h. The temperature was maintained
25 between -70 to -85°C and was allowed to warm to room temperature and stand for 18h. The reaction was quenched by addition of acetic acid and concentrated under reduced pressure to afford an oily residuc.

The crude oil was taken up in acetone and 2,2-dimethoxypropane was added followed by catalytic amount of trifluoromethanesulfonic acid. The contents were stirred at room temperature for 4h and after the completion of the reaction was washed with bicarbonate solution. The organic extracts was washed with water and was concentrated to give an oil which was crystallized from hexane.

1.8 Preparation of (4R)-methyl 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-3-acetate (Formula VIII)

The crude mesylate from example 8 was taken up in methanol and NH_3 gas was bubbled. The contents were then stirred for 6-14h at room temperature. After the reaction was complete, solvent was removed under reduced pressure to afford the crude title compound of formula VIII.

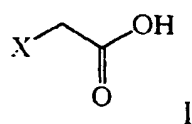
1.9 Preparation of [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[phenylaminocarbonyl]-1H-pyrrole-1-heptanoic acid, hemi calcium salt (Formula XXII)

A solution of (4R)-methyl 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-3-acetate (of formula XIV) and 4-fluoro- α -[2-methyl-1-oxopropyl]- γ -oxo-N- β -diphenylbenzenebutaneamide (formula XVII) and acetic acid in xylene were heated to reflux to 44h. The solution was diluted with diisopropyl ether and methanol and was washed with dilute methanolic sodium hydroxide solution, dilute HCl and the solvent was then removed under vacuum. The crude oil was stirred with moist silica in CH_2Cl_2 and was stirred at room temperature for 18h. A solution of aqueous NaOH was then added at room temperature and was stirred for 4h. The reaction mixture was diluted

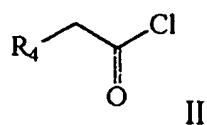
with water and was washed with diisopropyl ether. The aqueous layer was acidified with HCl and was taken up in diisopropyl ether. The crude acid intermediate was then taken up in EtOAc and NH_3 gas was bubbled. The contents were stirred for completion of the reaction and
5 solvent was removed upon which the product crystallized. The crude ammonium salt is then taken up in diisopropyl ether-isopropanol mixture and a solution of calcium acetate was added at room temperature upon which the calcium salt precipitated from the solution. The product was filtered and dried under vacuum to get
10 formula XXII of acceptable pharmaceutical purity.

The invention has been described by reference to specific embodiments, this was for the purpose of illustration only. Numerous alternative embodiments will be apparent to those skilled in the art and are considered within the scope of these claims.

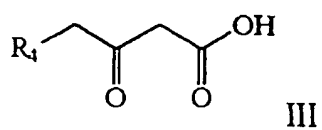
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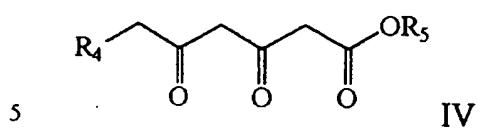
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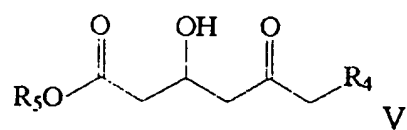
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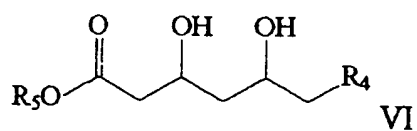
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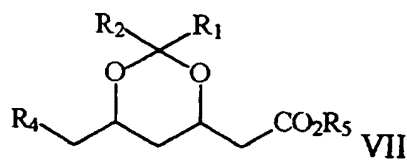
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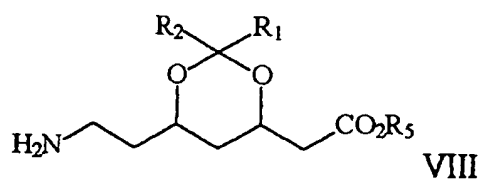
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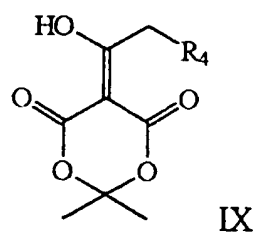
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VII

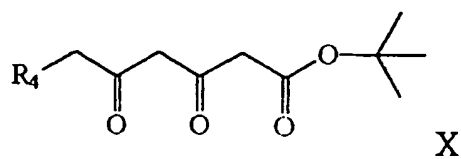


VIII

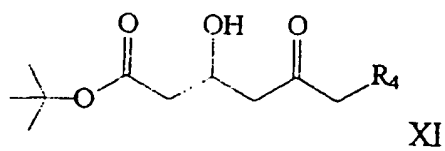


IX

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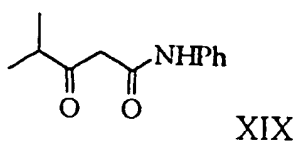
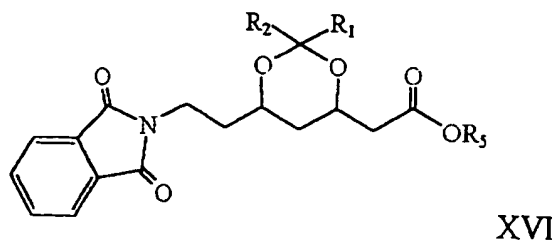
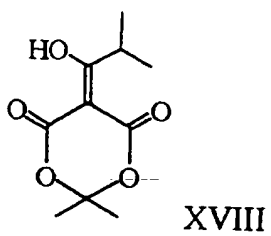
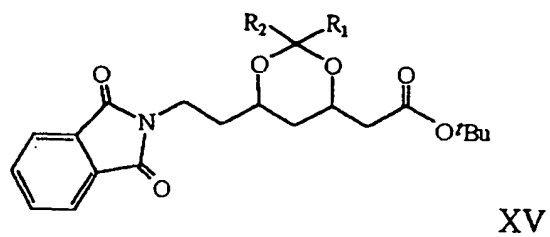
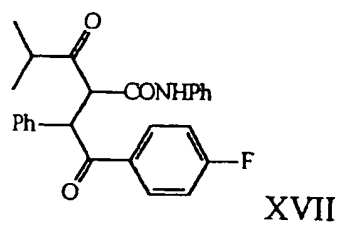
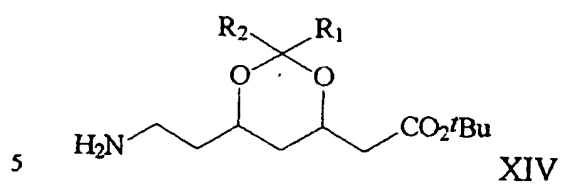
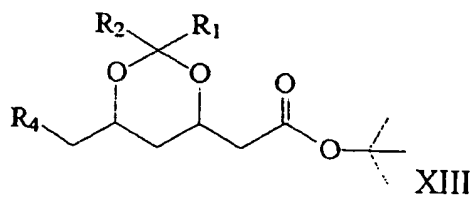
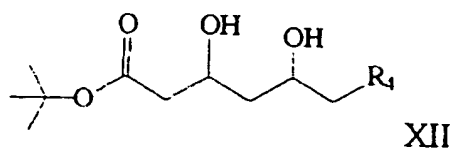


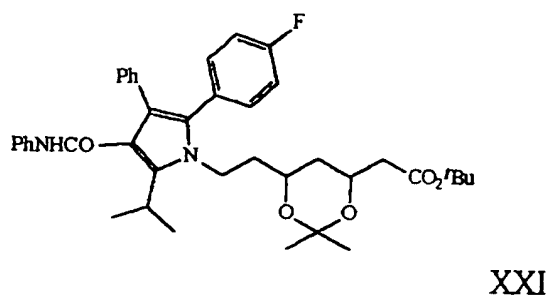
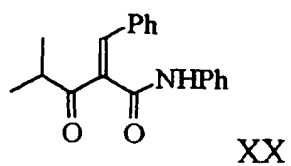
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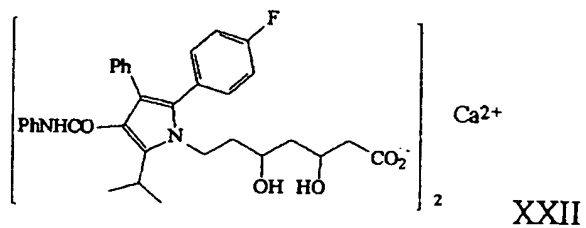
XI

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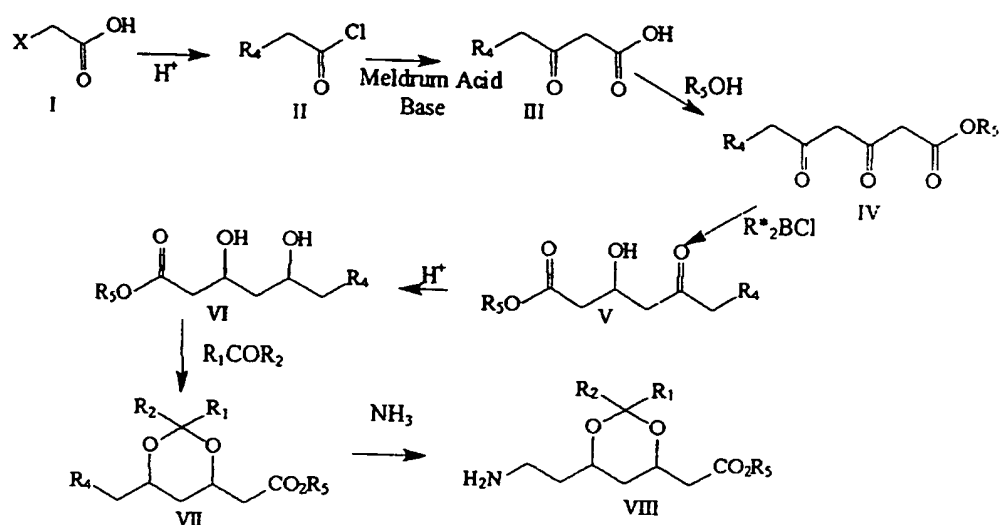




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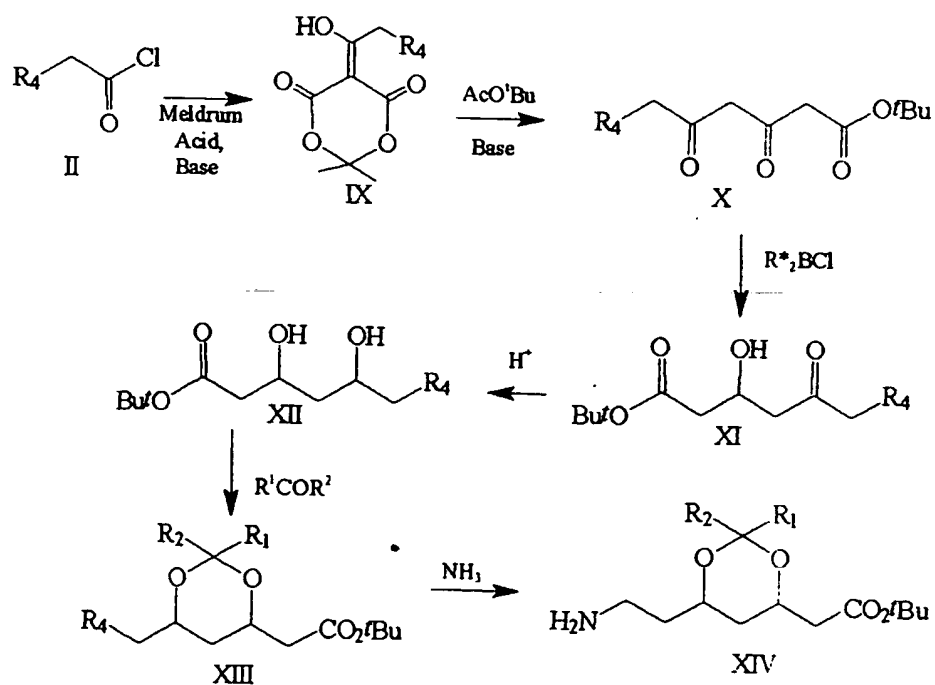


Scheme -1

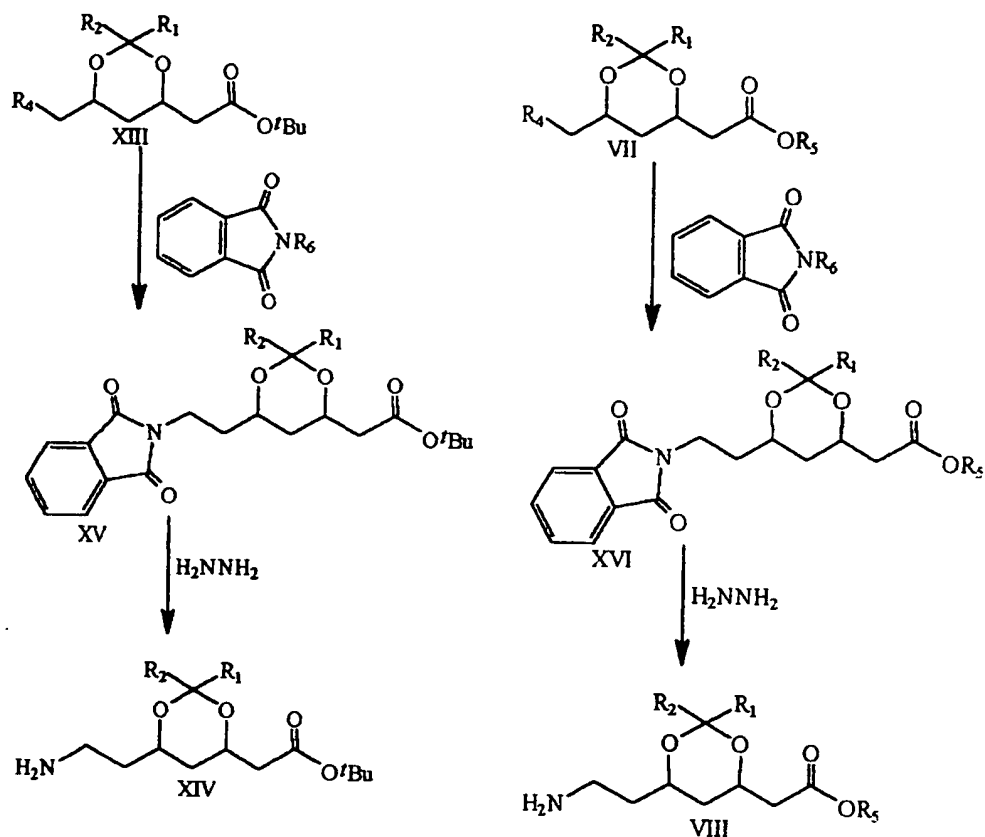


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Scheme -2

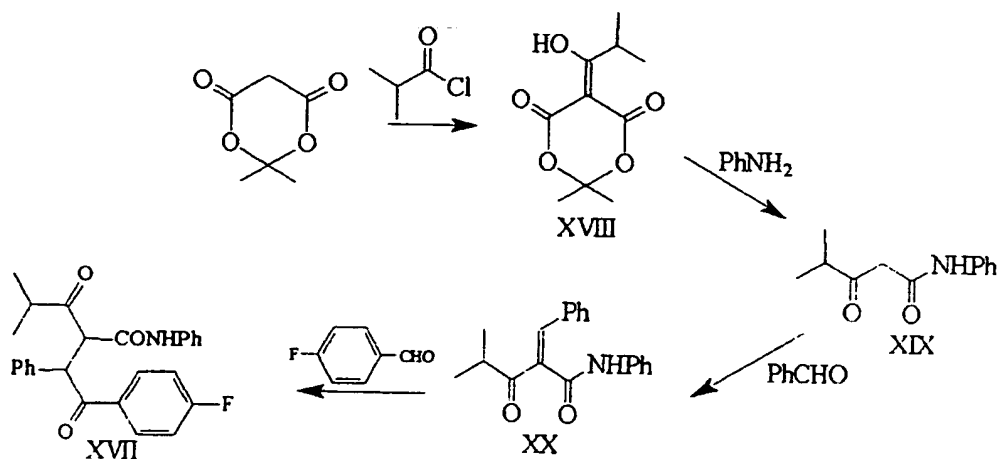


Scheme - 3

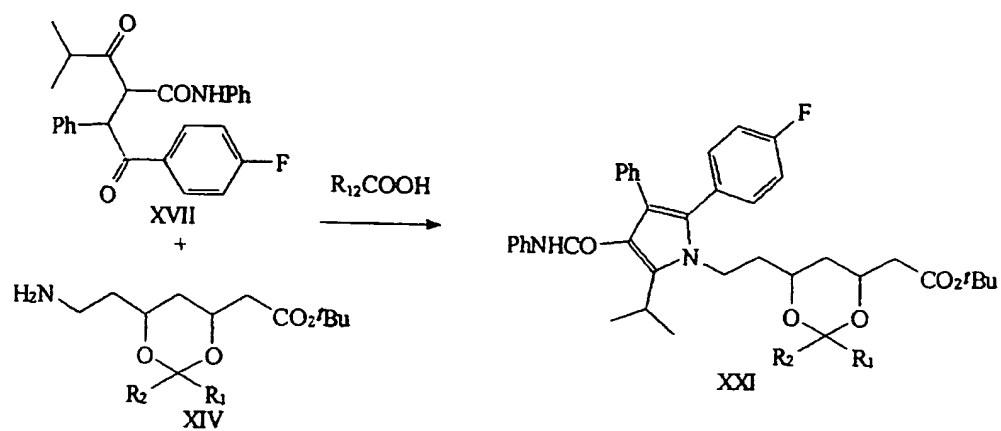


Scheme - 4

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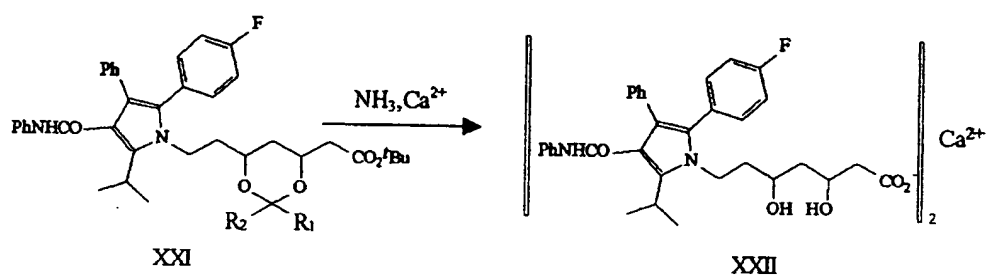


Scheme – 5



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Scheme - 6



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We claim:

1. The process involves the synthesis of compound R-(R*,R*)]-2-(4-fluorophenyl)-B,D-dihydroxy-5-(1-methylethyl)-3-phenyl-4-
5 [(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (formula XXII) which comprising:
 - a) reacting of compound of formula XVII with a compound of structure XIV in a non-polar solvent, to give an intermediate of structure XXI,
 - 10 b) deprotection, followed by hydrolysis of the compound of structure XXI followed by cyclization in ethyl acetate to give the lactone,
 - c) treating the lactone with NH₃ to give the ammonium salt, and
 - 15 d) reacting the ammonium salt with CaCl₂ gives the corresponding calcium salt of formula XXII.
2. A process as claimed in claim 1, wherein the non-polar solvent in step (a) is selected from xylene or acetonitrile.
3. A process as claimed in claim 1, wherein the de-protecting
20 agent in step (b) is selected from moist silica or PTSA.
4. A process as claimed in claim 1, wherein the ammonium salt in step (c) is prepared by treating with aqueous NH₃ or methanolic NH₃ or by passing NH₃ gas to the compound taken in EtOAc, MeOH, isopropyl alcohol, diisopropyl ether or cyclohexane.
- 25 5. A process as claimed in claim 1, wherein the compound of compound of formula XVII is prepared by:
 - a) reacting meldrum acid with isobutyryl chloride in the presence of base in CH₂Cl₂ to give an intermediate of formula XVIII,

- b) reacting the intermediate of formula XVIII with base in CH_2Cl_2 to give an intermediate of formula XIX,
- c) reacting the intermediate of formula XIX with benzaldehyde in the presence of base and toluene to give a compound
5 of formula XX, and
- d) reacting of compound of formula XX with 4-fluorobenzaldehyde with a metal cyanide and polar solvent in the presence of a base to give the compound of formula XVII.
6. A process as claimed in claim 5 where in step (b) the base is
10 selected from aniline, pyridine, triethylamine, dimethylaniline, diethylisopropylamine.
7. A process as claimed in claim 5 where in step (c) the base is selected from piperidine, pyrrolidine or diisopropylethylamine.
8. A process as claimed in claim 5 where in the metal cyanide in
15 step (d) is selected from NaCN, CuCN, KCN, AgCN or tetraalkyl ammonium cyanide.
9. A process as claimed in claim 5 wherein the polar solvent in step (d) is selected from DMSO, DMF, CH_3CN .
10. A process as claimed in claim 5 wherein the base in step (d) is
20 selected from diisopropylethyl amine, 1-methylimidazole, pyridine.
11. A process as claimed in claim 1 wherein compound of (4R)-methyl 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-3-acetate (Formula XIV) used in step (a) is prepared by:
- a) reacting a compound of formula II with meldrum's acid
25 followed by hydrolysis to give a compound of formula III,
- b) reacting a compound of formula III with thionyl chloride to give an acid chloride which is then reacted with a meldrum's acid followed by alcoholysis to give a compound of formula IV,

- c) reducing a compound of formula IV to give a compound of formula V,
 - d) reducing a compound of formula V to give a dihydroxy ester of formula VI,
 - 5 e) Converting a compound of formula VI to give a compound of formula VII,
 - f) ammonolysis of a compound of formula VII to give a compound of formula VIII,
 - g) alternatively reacting the compound of formula VII with
10 phthalimide salt to give a compound of formula XVI,
 - h) reacting a compound of formula XVI with hydrazine hydrate to give the compound of formula VIII, and
 - i) where R_5 = ter-butyl in formula VIII, formula XIV is obtained
- 15 12. A process as claimed in claim 11 wherein R_4 in step (a) is chosen from, OMs, OTs, Br, Cl or I.
13. A process as claimed in claim 11 wherein, the alcohol in step (b) is chosen from methanol, ethanol, isopropanol, benzyl alcohol.
14. A process as claimed in claim 11 wherein the reducing agent in
20 step (c) is baker's yeast or a reagent of formula R^*_2BCl where R^*_2 is chosen from (-) α pinene or (+) - α - pinene.
15. A process as claimed in claim 11 wherein the reducing agent in step (d) is chosen from dimethoxyethylboron or triethoxyboron and sodium borohydride.
- 25 16. A process as claimed in claim 11 wherein the protecting group for conversion in step (e) is chosen from acetone, benzophenone, acetophenone or benzaldehyde.
17. A process as claimed in claim 11 wherein the reagent for ammonolysis in step (f) is chosen from aqueous NH_3 , methanolic NH_3

or gaseous NH_3 in a solvent chosen from EtOAc, cyclohexane, methanol, isopropanol or diisopropyl ether.

18. A process as claimed in claim 11 wherein the phthalimide salt in step (g) is chosen from potassium, sodium or lithium.

5 19. A process as claimed in claim 1 wherein compound of (4R)-methyl 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-3-acetate (Formula XIV) used in step (a) is prepared by:

a) reacting a compound of formula II with meldrum's acid followed by hydrolysis to give a compound of formula IX,

10 b) reacting a compound of formula IX with tert-butyl acetate with a base at -30 to -80°C to give a compound of formula X,

c) reducing a compound of formula X to give a compound of formula XI,

d) reducing a compound of formula XI to give a dihydroxy ester of formula XII,

e) Converting a compound of formula XII to give a compound of formula XIII,

f) ammonolysis of a compound of formula XIII to give a compound of formula XIV

20 g) alternatively reacting the compound of formula XIII with phthalimide salt to give a compound of formula XV and

h) reacting a compound of formula XV with hydrazine hydrate to give the compound of formula XIV.

25 20. A process as claimed in claim 19 wherein R_4 in step (a) is chosen from, OMs, OTs, Br, Cl or I.

21. A process as claimed in claim 19 wherein the reducing agent in step (c) is baker's yeast or a reagent of formula R^*_2BCl where R^*_2 is chosen from (-) α pinene or (+) $-\alpha$ - pinene.

22. A process as claimed in claim 19 wherein the reducing agent in step (d) is chosen from dimethoxyethylboron or triethoxyboron and sodium borohydride.
23. A process as claimed in claim 19 wherein the protecting group
5 for conversion in step (e) is chosen from acetone, benzophenone, acetophenone or benzaldehyde.
24. A process as claimed in claim 19 wherein the reagent for ammonolysis in step (f) is chosen from aqueous NH_3 , methanolic NH_3 or gaseous NH_3 in a solvent chosen from EtOAc, cyclohexane,
10 methanol, isopropanol or diisopropyl ether.
25. A process as claimed in claim 19 wherein the phthalimide salt in step (g) is chosen from potassium, sodium or lithium.
26. The intermediate compound of formula XVIII as claimed in claim 5.
- 15 27. The intermediate of formula XIV as claimed in claim 1.
28. The intermediate of formula XV as claimed in claim 19.
29. The intermediate of formula VII, wherein R_5 is chosen from C_1 - C_5 alkyl, benzyl, isopropyl, cyclohexyl or tert-butyl as claimed in claim 11.
- 20 30. The intermediate of formula IX, wherein R_4 is chosen from CH_2Br , CH_2Cl , CH_2I , CH_2OMs or CH_2Ots as claimed in claim 19.

AMENDED CLAIMS

[received by the International Bureau on 16 February 2001 (16.02.01);
original claims 1-30 replaced by new claims 1-21 (5 pages)]

- 5 1. The process for the manufacture of compound R-(R*, R*)]-2-) 4-fluorophenyl)-
β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-
pyrrole-1-heptanoic acid hemi calcium salt (formula XXII) which comprises:
- 10 a) reacting of compound of formula XVII with a compound of structure
XIV or a compound of structure VIII in a mixture of solvents chosen
from xylene, cyclohexane, methyl tert-butyl ether, diisopropyl ether,
acetonitrile, in the presence of catalyst chosen from trifluoromethyl
sulfonic acid, methane sulfonic acid, p-toluene sulfonic acid (PTSA) or
15 pyridine p-toluene sulphonic acid (PPTS), to give an intermediate of
structure XXI, where R₁ or R₂ is independently from H, C₁ to C₃ alkyl,
phenyl, benzyl, substituted phenyl and R₅ is chosen from C₁-C₆ n-alkyl,
C₃-C₆ Cycloalkyl, benzyl or ter-butyl,
- 20 b) deprotection followed by hydrolysis of the compound of structure XXI
followed by cyclization in ethyl acetate to give the lactone,
- c) treating the lactone with NH₃ to give the ammonium salt, and
- 25 d) reacting the ammonium salt with Ca⁺² salts gives the corresponding
calcium salt of formula XXII.
2. A process as claimed in claim 1, wherein the ammonium salt in step (c) is
prepared by treating with aqueous NH₃ or methanolic NH₃ or by passing NH₃
30 gas to the compound taken in EtOAc, MeOH, Isopropyl alcohol, diisopropyl
ether or cyclohexane.
3. A process as claimed in claim 1, wherein the compound of formula XVII is
prepared by:
- 35 a) reacting meldrum acid with isobutyryl chloride in the presence of base in
CH₂Cl₂ to give an intermediate of formula XVIII.
- b) reacting the intermediate of formula XVIII with aniline in CH₂Cl₂ to give
40 an intermediate of formula XIX,

- 5 c) reacting the intermediate of formula XIX with benzaldehyde in the presence of catalyst and toluene to give a compound of formula XX, and
- d) reacting of compound of formula XX with 4-fluorobenzaldehyde with a cyanide reagent and solvent in the presence of a base to give the compound of formula XVII.
- 10 4. A process as claimed in claim 3 wherein step (c) the catalyst is selected from piperidine, pyrrolidine, diisopropylethylamine, PTSA or PPTS.
- 15 5. A process as claimed in claim 3 where in the cyanide reagent in step (d) is selected from NaCN, CuCN, KCN, AgCN, tetra-alkyl ammonium cyanide or trimethyl silyl cyanide.
6. A process as claimed in claim 3 wherein the solvent in step (d) is selected from DMSO, DMF, CH₃CN.
- 20 7. A process as claimed in claim 3 wherein the base in step (d) is selected from diisopropylethyl amine, 1-methylimidazole, pyridine.
- 25 8. A process as claimed in claim 1 wherein compound of formula XIV used in step (a); where R₁ or R₂ is independently from H, C₁ to C₃ alkyl, phenyl, benzyl, substituted phenyl and R₄ is chosen from CH₂OMs, CH₂OTs, CH₂Cl, CH₂Br or CH₂I; is prepared by:
- 30 a) reacting a compound of formula II, with meldrum's acid followed by hydrolysis to give a compound of formula IX,
- b) reacting a compound of formula IX with ter-butyl acetate with a base at -30 to -80 °C to give a compound of formula X,
- 35 c) reducing a compound of formula X to give a compound of formula XI.
- d) reducing a compound of formula XI to give a dihydroxy ester of formula XII,
- 40 e) converting a compound of formula XII to give a compound of formula XIII.

- 5 f) ammonolysis of a compound of formula XIII to give a compound of formula XIV.
- g) alternatively reacting the compound of formula XIII with phthalimide salt to give a compound of formula XV, and
- 10 h) reacting a compound of formula XV with hydrazine hydrate to give the compound of formula XIV.
9. A process as claimed in claim 8 wherein the reducing agent in step (c) is derived from yeast or a reagent of formula R^*_2BCl , where R^*_2 is chosen from α pinene.
- 15 10. A process as claimed in claim 8 wherein the reducing agent in step (d) is chosen from dimethoxyethylboron or triethoxyboron and sodium borohydride.
- 20 11. A process as claimed in claim 8 wherein the reagent for ammonolysis in step (f) is chosen from aqueous NH_3 , methanolic NH_3 or gaseous NH_3 in a solvent chosen from EtOAc, cyclohexane, methanol, isopropanol or diisopropyl ether.
- 25 12. A process as claimed in claim 8 wherein the phthalimide salt in step (g) is chosen from potassium, sodium or lithium.
- 30 13. A process as claimed in claim 1 wherein compound of formula VIII used in step (a); where R_1 or R_2 is independently from H, C_1 to C_3 , alkyl, phenyl, benzyl, substituted phenyl R_4 is chosen from CH_2OMs , CH_2OTs , CH_2Cl , CH_2Br or CH_2I and R_5 is C_1 - C_6 n-alkyl, C_3 - C_6 cycloalkyl, benzyl or ter-butyl; is prepared by:
- 35 a) reacting a compound of formula II, with meldrum's acid followed by hydrolysis to give a compound of formula III,
- b) reacting a compound of formula III with thionyl chloride to give an acid chloride which is then reacted with a meldrum's acid followed by alcoholysis to give a compound of formula IV,
- 40 c) reducing a compound of formula IV to give a compound of formula V.

- 5 d) reducing a compound of formula V to give a dihydroxy ester of formula VI,
- e) converting a compound of formula VI to give a compound of formula VII.
- 10 f) ammonolysis of a compound of formula VII to give a compound of formula VIII.
- g) alternatively reacting the compound of formula VII with phthalimide salt to give a compound of formula XVI, and
- 15 h) reacting a compound of formula XVI with hydrazine hydrate to give the compound of formula VIII.

20 14. A process as claimed in claim 13 wherein the reducing agent in step (c) is derived from yeast or a reagent of formula R^*_2BCl , where R^*_2 is chosen from α pinene.

25 15. A process as claimed in claim 13 wherein the reducing agent in step (d) is chosen from dimethoxyethylboron or tetroxyboron and sodium borohydride.

16. A process as claimed in claim 13 wherein the reagent for ammonolysis in step (f) is chosen from aqueous NH_3 , methanolic NH_3 or gaseous NH_3 in a solvent chosen from EtOAc, cyclohexane, methanol, isopropanol or diisopropyl ether.

30 17. A process as claimed in claim 13 wherein the phthalimide salt in step (g) is chosen from potassium, sodium or lithium.

35 18. The intermediate of formula XVI, where R_1 or R_2 is independently from H, C_1 to C_3 alkyl, phenyl, benzyl, substituted phenyl and R_5 is chosen from $C_1 - C_6 n$ -alkyl, $C_3 - C_6$ cycloalkyl, benzyl or ter-butyl.

19. The intermediate of formula XV, where R_1 or R_2 is independently from H, C_1 to C_3 alkyl, phenyl, benzyl, substituted phenyl.

20. The intermediate of formula VII, where R_1 or R_2 is independently from H, C_1 to C_3 alkyl, phenyl, benzyl, substituted phenyl and R_4 is chosen from CH_2Br , CH_2Cl , CH_2I , CH_2OMs or CH_2OTs and R_5 is chosen from $C_1 - C_6$ n alkyl, $C_3 - C_6$ cycloalkyl, benzyl or ter-butyl.
21. The intermediate of formula IX, wherein R_4 is chosen from CH_2Br , CH_2Cl , CH_2I , CH_2OMs or CH_2OTs .

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/IN 00/00030

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D207/34 C07D319/06 C07D405/06 A61K31/40 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BAUMANN K L ET AL: "THE CONVERGENT SYNTHESIS OF CI-981, AN OPTICALLY ACTIVE, HIGHLY POTENT, TISSUE SELECTIVE INHIBITOR OF HMG-COA REDUCTASE" TETRAHEDRON LETTERS, NL, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 33, no. 17, 21 April 1992 (1992-04-21), pages 2283-2284, XP000608147 ISSN: 0040-4039 the whole document	1-10
X	EP 0 330 172 A (WARNER LAMBERT CO) 30 August 1989 (1989-08-30) cited in the application Scheme III and V page 6, line 44 -page 11, line 18 --- -/-	1-10

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

15 November 2000

Date of mailing of the international search report

24/11/2000

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Seitner, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IN 00/00030

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>ZAWACKI F J ET AL: "A Convenient Synthesis of Unsymmetrical, Substituted gamma-Pyrones from Meldrum's Acid" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 37, no. 36, 2 September 1996 (1996-09-02), pages 6499-6502, XP004030727 ISSN: 0040-4039 Scheme 2 compound 5 -----</p>	26

INTERNATIONAL SEARCH REPORT

International Application No. PCT/IN 00 00030

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 11-18, 19-25, 27-29

Claims 11-18, 19-25, and 27-29 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The following functional statements do not enable the skilled person to determine which technical features are necessary to perform the stated functions:

In claims 11-18 no definitions have been provided for R1, R2, R4, and/or R5.

In claims 19-25 no definitions have been provided for R1, R2, and/or R4.

In claims 12 and 20 the definitions of R4 seem to be incorrect.

In claims 27-29 R1 and R2 have not been defined.

Furthermore, in claim 29 R4 has not been defined.

Due to the lack of clarity within the meaning of Article 6 PCT a meaningful search of the claims 11-18, 19-25, 27-29 is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, namely claims 1-10 and claims 26 and 30.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IN 00/00030

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